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Murine typhus in central Greece: epidemiological, clinical, laboratory, and therapeutic-response features of 90 cases

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SUMMARY

Objectives: To document and evaluate the clinico-epidemiological profile of murine typhus during the re-emergence of the disease in a previously endemic focus in central Greece.

Methods: This was a 5-year, hospital-based, observational study, in which 90 adult patients with murine typhus were prospectively identified and studied.

Results: Most cases of the disease occurred in rural (52%) and semi-urban (34%) settings, with a seasonal frequency peak during the late summer. The triad of fever, headache, and rash was present in 64% of the patients within 2 days of hospital admission. Normal white blood cell counts (63%), thrombocytopenia (81%), and a high erythrocyte sedimentation rate (93%) were the main hematological findings upon presentation. Elevated aminotransferases (>84%), hypoalbuminemia (81%), and hyponatremia (36%) were prominent biochemical abnormalities. Pulmonary, neurological, and renal complications were noted in 26% of the patients and subsided after specific treatment. The duration of fever was shorter in patients treated with doxycycline (median 3 days) compared to ofloxacin ($p = 0.001$) or doxycycline plus ofloxacin ($p = 0.009$).

Conclusions: Murine typhus has the potential to cause significant morbidity. Awareness of the disease in endemic areas, early recognition of its clinical and laboratory features, and prompt administration of effective treatment are key factors to prevent potentially severe complications.

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1. Introduction

Murine or endemic typhus (MT) is a flea-borne illness caused by *Rickettsia typhi*, an obligate intracellular parasite that lives in the cytoplasm of the cells of the host.^{1,2} The classical transmission cycle for MT is rat–flea–rat, with commensal rats of the subgenus *Rattus* (*R. norvegicus* and *R. rattus*) and their fleas (*Xenopsylla cheopis*) acting as the main reservoir and vector, respectively.^{1–3} Rats also serve as amplifying hosts by making *R. typhi* in their blood available for the fleas, which transmit the organism back to rats during subsequent feeding.^{1,2} Humans are accidental hosts who presumably become infected when *R. typhi*-infected flea feces contaminate a pruritic flea-bite wound or the conjunctivae of the host, or the respiratory tract via inhalation of dust containing infective material.^{1–3} Transmission by different flea species (the cat flea, *Ctenocephalides felis*) and from different reservoirs (domestic cats and opossums) have been well documented in some areas.⁴

The clinical diagnosis of MT is challenging because the illness presents with many non-specific symptoms and signs, and confirmation by serology may be too late to affect the clinical decision.^{1–4} The clinical course varies from mild symptoms that may not require hospitalization to severe illness that can result in death. Disease severity has been associated with older age, delayed diagnosis and treatment, glucose-6-phosphate dehydrogenase deficiency, hepatic and renal dysfunction, central nervous system abnormalities, and pulmonary compromise.^{2–4} Untreated patients present symptoms and signs for 2–3 weeks, with up to 10% requiring intensive care.^{3,4} The case fatality rate, although low with the use of appropriate antibiotics (1%), can approach 4% in the absence of specific treatment.⁴

MT occurs in environments ranging from hot and humid to cold and montane or semiarid, but it is most prevalent in warm areas, particularly in port cities and coastal urban regions, where high populations of rodents are found.^{1–5} Endemic foci of MT remain in the Mediterranean region, the southern USA, Southeast Asia, and Western Australia.^{1–5} Sporadic cases and outbreaks of MT have been reported worldwide, frequently involving travelers returning from endemic areas.⁶ MT has been reported to have re-emerged in formerly endemic areas,^{7–11} and it was recently

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seen to emerge in areas not previously known to be endemic for this disease.^{12–14}

MT re-emerged in Greece after four decades of absence, when 49 cases of the disease were reported on the island of Evia in central Greece in 1985.¹⁵ The number of patients with MT who were referred to the local hospital gradually diminished over the following years and the disease was almost forgotten. However, new cases of MT were again diagnosed on Evia in 1998. We therefore conducted a 5-year, hospital-based, prospective surveillance study to re-evaluate the evolution of epidemiological, clinical, and therapeutic aspects of MT in the region, and to warn physicians and the public health authorities of the re-emergence and persistence of the disease in central Greece.

2. Patients and methods

2.1. Study population

We performed a 5-year prospective case-series study at the General Hospital of Chalkida, a 200-bed tertiary-care institution that serves a population of over 200 000 people on the island of Evia in central Greece.

Our reference population included adult patients (≥ 18 years old) for whom there was a clinical suspicion of MT and who were admitted to the hospital between 2001 and 2005. The minimum presumptive clinical criteria for MT were the presence of fever ($\geq 38^\circ\text{C}$) and/or headache and/or skin rash, and the absence of any other clinically identified cause of infection (e.g., pneumonia, urinary tract or gastrointestinal infection). Three serum samples were obtained from each patient suspected of being infected (on admission, at 1 week after admission, and 3 weeks later) and were assayed for the presence of antibodies against *R. typhi* by the indirect immunofluorescent antibody (IFA) test. IgG titers of $\geq 1:960$ or IgM titers of $\geq 1:400$ and/or a four-fold increase in the titers between two successive assays were considered as indicative of acute infection. A case of MT was defined as a patient meeting the minimum presumptive clinical criteria and having IFA confirmation. Serology was performed at the Laboratory of Clinical Bacteriology, Parasitology, Zoonoses and Geographical Medicine of the University of Crete.

Data collected and analyzed for each case of MT included demographic and epidemiologic characteristics (date of hospital admission, age, gender, occupation, and area of residence), symptoms, signs and complications during the course of illness, routine laboratory test results on admission, treatment data (antibiotic regimen and time to defervescence), and outcome.

2.2. Statistical analysis

Categorical data are presented as counts and percentages. Continuous data are reported as the mean value \pm standard deviation (SD) or median value and interquartile range (IQR), depending on the degree of skewness in the distributions. For log-normally distributed data (such as serologic data), the geometric mean and geometric standard deviation are used to summarize location and dispersion. Continuous data were compared between different patient groups using the unpaired *t*-test or the Mann–Whitney test and categorical data were compared by use of the Chi-square test or Fisher's exact test where appropriate. Time-to-event data were analyzed by Kaplan–Meier survival analysis and the log-rank test. Ninety-five percent confidence intervals (95% CI) were calculated when appropriate. A *p*-value of less than 0.05 (two-tailed) was considered to indicate statistical significance. The data analysis was performed using SPSS version 16 (SPSS, Inc., Chicago, IL, USA).

3. Results

3.1. Demographic and epidemiological features

Of the 174 patients who were suspected of MT during the 5-year study period, 90 (51.7%) were confirmed to have the disease and were included in the study. The median patient age was 43 years (IQR 33–62, range 18–89 years) and 61 patients (67.8%) were male.

The overall cumulative incidence of the disease was 0.43 cases per 100 adult patients and 2.36 cases per 100 adult patients with an acute-febrile illness who were admitted to the hospital during the study period. Cases occurred throughout the year, but a seasonal frequency peak was evident during the late summer (Figure 1). All patients originated from within a 30-km area surrounding the city of Chalkida, most frequently residing in rural (52.2%) or semi-urban (34.4%) settings. Most patients were farmers (40%), outdoor laborers and construction workers (14.4%), or housewives (17.8%).

3.2. Clinical manifestations

The earliest symptom of illness was an abrupt onset of fever in all cases, usually associated with chills (91.1%). Fever was continuous and began a median of 3 days (IQR 2–4 days, range 2–6 days) before hospital admission. The maximum temperature recorded upon presentation ranged from 38 to 41 $^\circ\text{C}$, with a mean of $39.5 \pm 0.5^\circ\text{C}$. The median total duration of fever was 7 days (IQR 6–8 days, range 5–10 days).

A frontal headache was noted for 79 (87.8%) patients; it began a median of 2 days after the onset of fever (IQR 1–2, range 1–4 days) and lasted for a median of 4 days (IQR 4–5, range 3–7 days). A rash was noted for 62 (68.9%) patients; this was macular or maculopapular, with a centrifugal spread over the trunk, sparing the palms and soles. Rash began a median of 4 days after the onset of fever (IQR 3–4, range 2–5 days) and lasted for a median of 3 days (IQR 3–3, range 2–4 days). The classical triad of fever, headache, and rash was present in 58 (64.4%) of the patients during their illness; however 25 (27.8%) patients exhibited two of these signs and seven (7.8%) had fever only. Other symptoms such as malaise, anorexia, myalgia, arthralgia, nausea/vomiting, etc. were less common. Sixteen patients (17.8%) had both spleen and liver enlargement, while isolated liver or spleen enlargement was

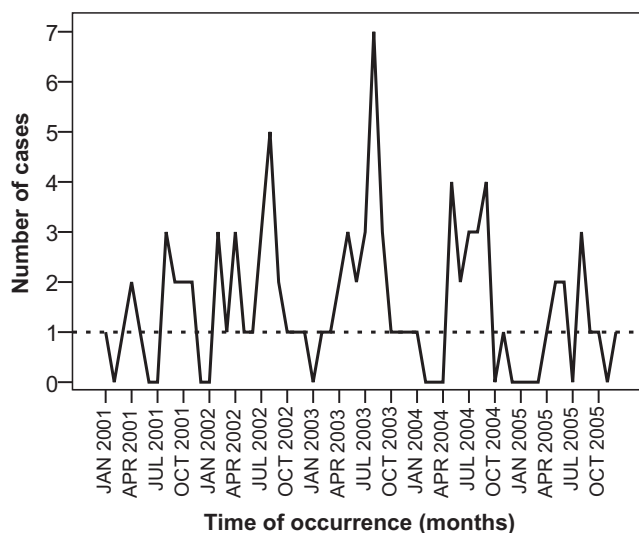


Figure 1. Monthly distribution of cases of murine typhus in central Greece (the horizontal reference line (dotted) corresponds to the series median).

Table 1

Clinical manifestations in 90 patients with murine typhus in central Greece

Clinical manifestations	No. (%) of patients
Symptoms	
Fever	90 (100)
Chills	82 (91.1)
Headache	79 (87.8)
Perspiration	76 (84.4)
Malaise	62 (68.9)
Anorexia	50 (55.6)
Myalgia	49 (54.4)
Arthralgia	33 (36.7)
Nausea/vomiting	30 (33.3)
Non-productive cough	29 (32.2)
Signs	
Rash	62 (68.9)
Hepatomegaly	29 (32.2)
Splenomegaly	23 (25.6)
Conjunctivitis	19 (21.1)
Complications	
Pulmonary involvement	15 (16.7)
Central nervous system involvement	10 (11.1)
Acute renal failure	7 (7.8)
Disseminated intravascular coagulation	2 (2.2)

observed in 13 (14.4%) and in seven (7.8%) patients, respectively. Clinical manifestations in the 90 patients are shown in Table 1.

The clinical course was complicated in 23 patients (25.6%) who presented a total of 34 complications, including pulmonary involvement in 15 cases (13 interstitial infiltrations and two plural effusions), central nervous system involvement in 10 cases (eight stupor and two coma), acute renal failure in seven cases, and disseminated intravascular coagulation in two cases. Patients who presented these complications were significantly older than those without complications (median (IQR) age, 65 (51–71) vs. 42 (28–52), respectively, $p < 0.001$), while no difference according to gender was observed (men, 69.6% vs. 67.2%, respectively, $p = 0.832$).

3.3. Laboratory findings

Laboratory test results upon admission are summarized in Table 2. Twenty-eight patients (31.1%) displayed anemia upon admission. Only four patients (4.4%) had leukocytosis, but

leukopenia was present in 29 cases (32.2%). Thrombocytopenia was noted for 73 patients (81.1%). A high erythrocyte sedimentation rate was observed for 84 patients (93.3%).

The most prominent biochemical findings on admission were hypoalbuminemia for 73 patients (81.1%) and a >1-fold elevation of aspartate aminotransferase and alanine aminotransferase observed in 76 (84.4%) and 79 patients (87.8%), respectively. Significant abnormalities in serum electrolyte values included hyponatremia in 32 (35.6%) and hypokalemia in 13 (14.4%) patients.

IFA test results in three serum samples taken on admission (median 3 days, range 2–6 days after onset of fever), 1 week after admission, and 3 weeks later, respectively, are shown in Table 3. Serological confirmation of MT was met for 14 patients (15.6%) in the first sample, 90 patients (100%) in the second sample, and 69 patients (76.7%) in the third sample. When serology data were examined by age, none of the elderly patients (age ≥ 65 years) had an IgG or IgM titer exceeding the cut-off titer during the first week of illness. In contrast, 20% of the non-elderly patients had a serological confirmation within the first week of illness. No age-related difference in antibody kinetics was observed in the second and third serum samples. No association of the IFA antibody titers with the presence of complications was observed.

3.4. Response to treatment and outcome

All patients received treatment on the day of admission: 73 patients (81.1%) were treated with doxycycline, 11 (12.2%) with ofloxacin, and six patients (6.7%) received doxycycline plus ofloxacin. Median times between the onset of fever and initiation of treatment were similar for the three treatment options used: 3 days (range 2–6 days) for doxycycline, 3 days (range 2–5 days) for ofloxacin, and 3.5 days (range 2–4 days) for doxycycline plus ofloxacin ($p = 0.216$).

Fever returned to normal in a median of 3 days with doxycycline (95% CI 2.8–3.2 days), 4 days with ofloxacin (95% CI 3.8–4.2 days), and 4 days with doxycycline plus ofloxacin (95% CI 3.6–4.4 days). Comparison of the three treatment groups using a Kaplan–Meier survival analysis (Figure 2) showed that time to defervescence was significantly shorter in the group of patients treated with doxycycline compared to those treated with ofloxacin ($p = 0.001$) or those treated with doxycycline plus ofloxacin

Table 2

Laboratory findings on admission in 90 patients with murine typhus in central Greece

Laboratory findings	Median (IQR)	Range	Reference cut-off ^a	
			Value	No. (%)
Blood cell examination				
White blood cells ($\times 10^9/l$)	4.6 (3.8–6.2)	1.7–13.0	<4	29 (32.2)
Hemoglobin (g/dl)	12.3 (11.5–13.7)	8.7–16.3	<12	28 (31.1)
Platelets ($\times 10^9/l$)	126.5 (97–146)	34–510	<150	73 (81.1)
Erythrocyte sedimentation rate (mm/h)	38 (32–52)	15–110	>20	84 (93.3)
Biochemical examination				
Albumin (mg/dl)	3.4 (3.2–3.6)	2.7–4.6	<38	73 (81.1)
Creatinine (mg/dl)	1.1 (0.9–1.2)	0.6–3.7	>1.3	12 (13.3)
Creatinine phosphokinase (U/l)	145.5 (128–176)	56–317	>170	28 (31.1)
Lactate dehydrogenase (U/l)	283 (230–373)	132–1386	>420	19 (21.1)
Aspartate aminotransferase (U/l)	52 (46–66)	21–253	>38	76 (84.4)
Alanine aminotransferase (U/l)	69 (56–87)	2.5–285	>41	79 (87.8)
γ -Glutamyl transferase (U/l)	57.5 (42–76)	13–397	>61	44 (48.9)
Total bilirubin (mg/dl)	0.9 (0.7–1.2)	0.3–3.4	>0.6	79 (87.8)
Direct bilirubin (mg/dl)	0.3 (0.2–0.4)	0.0–3.1	>0.2	66 (73.3)
Total protein (g/dl)	6.2 (5.9–6.4)	3.9–6.9	<6	32 (35.6)
Potassium (mmol/l)	3.8 (3.6–4.2)	2.9–6.2	<3.6	13 (14.4)
Sodium (mmol/l)	136 (134–138)	127–146	<135	32 (35.6)

IQR, interquartile range.

^a Number and percentage of patients with values below or above the normal cut-off value as indicated.

Table 3Indirect fluorescent antibody test results in 90 patients with murine typhus in central Greece^a

	First serum sample		Second serum sample		Third serum sample	
	IgM	IgG	IgM	IgG	IgM	IgG
Summary statistic: ^b						
Geometric mean (GSD)	134.7 (3.1)	321.6 (2.5)	620.5 (2.4)	2437.9 (2.4)	280.7 (1.8)	1045.2 (1.9)
Range	0–12 800	120–7680	200–12 800	480–61 440	50–3200	240–7680
No. (%) of patients with titers:						
Above the cut-off value ^c	11 (12.2)	12 (13.3)	83 (92.2)	89 (98.9)	34 (37.8)	67 (74.4)
Below the cut-off value, but four-fold increase in titers	–	–	3 (3.3)	1 (1.1)	0 (0)	0 (0)

GSD, geometric standard deviation.

^a Serum samples were taken at admission, at 1 week after admission and 3 weeks later.^b Data are inverse titer values.^c Cut-off values were IgM \geq 1:400 and IgG \geq 1:960.

($p = 0.009$). Differences in treatment effects remained consistent when patients were stratified by age group (based on quartile groupings) and gender.

The outcome was favorable for all patients and no relapse or death was observed within 6 months after discharge from the hospital.

4. Discussion

MT has a cosmopolitan distribution, and endemic foci of the disease are maintained worldwide. However, clinical studies of MT involving sufficiently large numbers of patients remain scarce.^{16–21} The disease is probably under-diagnosed and largely under-reported worldwide, due to its frequent mild course and non-specific presentation, the limited awareness of physicians, and because it is often not included in the list of nationally reportable diseases and is not actively monitored.^{1–5}

The present study, which is one of the largest case-series of MT reported to date, was a hospital-based active survey of MT, which re-emerged in a previously known endemic focus on the island of Evia. The classical rat–flea–rat transmission cycle of *R. typhi* has previously been confirmed in the study area, and the bacterium has been detected and identified in both rat blood samples and their fleas.^{22,23} An ecosystem favorable to the growth of rodent and flea populations and breaches in rodent control measures are most likely responsible for the re-emergence of MT in the region. Indeed, cases occurred throughout the year, with a seasonal frequency

peak in late summer in this study, when climatic conditions in the region are more favorable for the commensal rat population to flourish and human exposure to the environment is greater. In other studies, the highest incidence was observed in May and June,^{4,16,19} suggesting that climatic conditions are the main factors contributing to different seasonal distributions of human cases in different geographical areas.

Although MT has been described as a disease of mostly urban or port areas,^{1–3,6} most cases in the present study occurred in rural and semi-urban settings, with a peripheral distribution around the city of Chalkida. Moreover, most patients were men who had an occupation that required working outdoors in nature or were involved in agricultural activities, thus being at high risk for contact with rodents. Changes in vector–host ecology owing to environmental and human behavior modifications may be allowing the expansion of *R. typhi* into rural areas.²⁴ Regional studies in Spain noted that seroprevalence rates of *R. typhi* were not highest in urban areas,^{25–27} and a peri-domestic cycle involving dogs and wild rodents and their fleas was suggested to have contributed to the rural expansion of *R. typhi* in those regions.^{28,29} However, there is no evidence indicating that such a peri-domestic cycle may have been involved in our region.

We obtained three serum samples from each patient at various times after the onset of illness, which enabled us to depict antibody kinetics during the first month following disease onset. Within the first week of illness, the rates of serologic confirmation based on the IgM and IgG antibody levels were similar but very low in our patients. In contrast, almost all patients had IgM and IgG confirmatory levels within the second week following illness onset. Both IgM and IgG antibody levels had declined in the fourth week after onset, but the latter sustained confirmatory levels in a high proportion of the patients. These findings indicate that the IFA test is unhelpful for the diagnosis of MT early in the course of illness and that IgM antibody titers may not offer any advantage over IgG in the confirmation of the diagnosis. Moreover, a delay in the rise of antibody titers was noted for the elderly patients in this study, indicating that early laboratory confirmation of MT should not be expected in the elderly.

The clinical features of MT observed in this study were consistent with those reported by others,^{16–20,30,31} with fever, headache, and rash being the main and most frequent symptoms and signs. The frequency of rash in our patients (69%) was similar to that reported previously in our study region (71%),¹⁵ and within the range of that reported in other large regional cohorts in Greece, Spain, Croatia, and the USA (62–80%).^{18–20,30–32} The rash appeared a median of 4 days after onset of fever and lasted for a median of 3 days. Thus, the appearance and characteristics of rash may aid the early diagnosis of MT. In our patients the rash was macular or maculopapular with a centrifugal spread over the trunk, sparing

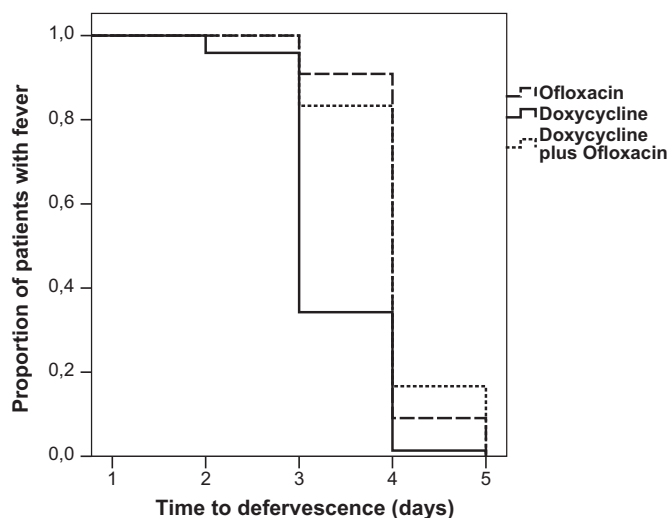


Figure 2. Kaplan–Meier plot of the relationship between antibiotics used and duration of fever in 90 patients with murine typhus in central Greece.

the palms and soles. Petechial lesions, which have scarcely been reported in the literature,^{18,19} were not observed in this study.

The usefulness of the classical triad of fever, headache, and rash as a clinical diagnostic tool for MT has been questioned by other researchers.¹⁹ However, our patients presented with continuous fever of abrupt onset, followed by frontal headache and then rash, with median time lags of 2 days between the onsets of each symptom. The clinical triad was completed in 64% of the patients within the first 2 days following admission. Thus, our data illustrate that the classical triad is a valuable early indicator of MT.

Several ocular manifestations associated with MT were recently reported in Tunisia.³³ We noted conjunctivitis in 21% of our patients. Therefore, complete ophthalmic examinations in patients suspected of MT may also be helpful in the early clinical diagnosis of the disease.

In agreement with other studies,^{16,18–21,30,31} we found that elevated aminotransferases and hypoalbuminemia were prominent biochemical abnormalities occurring in most of the patients. Hyponatremia, which has been reported with a varying frequency of 18% to 66% in other studies,^{16,19,20,30,31} was noted in 36% of our patients. *R. typhi*-induced systemic vasculitis allows extravasation of protein and electrolytes,² consistent with the hypoalbuminemia that was frequently observed. Elevation of aminotransferases is possibly due to hepatocyte and biliary injury adjacent to inflamed microvasculature.¹⁹

The main hematological findings observed in this study were also consistent with those noted by others,^{18,19,30,31} although their relative frequencies are greatly variable in the literature.³¹ Our patients presented mostly with normal white blood cell counts (63%), thrombocytopenia (81%), and a high erythrocyte sedimentation rate (93%). Thrombocytopenia, as well as leukopenia, is consistent with the consumption of platelets and leukocytes at the site of vascular inflammation.²

In general, MT is perceived as a mild disease. However, a significant proportion of our patients (26%), mainly elderly patients, presented one or more complications in different organs. A similarly high frequency of complications in patients with MT has been reported in Texas (27%).³⁴ These findings demonstrate that MT has the potential to cause significant morbidity.

Pulmonary involvement, mainly manifested with interstitial infiltrations, was noted in 17% of our patients, which is higher than usually reported (6–12%).^{18,35} Interstitial pulmonary infiltrates on chest radiography could be attributed to serum leakage from the damaged capillaries due to *R. typhi* invasion.²

Neurological findings have been reported in 15% to 45% of adult patients.^{16,19} In this study, 11% of the patients presented with stupor or coma. Aseptic meningitis and meningoencephalitis, which have infrequently been reported as delayed neurological manifestations of MT,³⁶ were not noted in our patients. Nevertheless, physicians practicing in or near *R. typhi*-endemic areas need to consider MT in the differential diagnosis of patients with fever, rash, and neurological manifestations.

Acute renal failure is not uncommon in patients with MT,^{20,31,34} and 8% of our patients had this complication. Renal failure could occur as a result of kidney hypoperfusion secondary to loss of intravascular volume through increased vascular permeability, or perivascular interstitial nephritis.²

Doxycycline is the drug of choice for MT in adults and children, excluding pregnant women.^{2,4} Large clinical series from Greece and the USA found that doxycycline resulted in a mean time to defervescence of 3 days,^{16,20} a finding that is also supported by the present study. Chloramphenicol is considered to be effective as an alternative antibiotic when doxycycline is contraindicated,^{2,4} but it is less efficient than doxycycline in terms of time to apyrexia,³⁷ and frequent relapses of the disease have been reported.³⁸ Quinolones are also considered to be acceptable alternatives.^{2–4} However,

ciprofloxacin has been noted to be less efficient than doxycycline with respect to duration of fever.³⁷ In this study, ofloxacin was found to be less efficient than doxycycline. Moreover, a poor response to ciprofloxacin in patients with MT has been reported,³⁹ and quinolone treatment was recently stated to have a 'deleterious effect' for the treatment of other rickettsial diseases.⁴⁰ Combinations of doxycycline with chloramphenicol or ciprofloxacin have also been used in clinical practice, but did not improve the effectiveness of doxycycline.³⁷ Similarly, in this study, ofloxacin plus doxycycline did not appear to provide any advantage over doxycycline alone in terms of duration of fever.

This study has certain limitations. First, it was a hospital-based study and a potential selection bias towards including more severe cases of MT may exist. Second, our case definition relied on serological testing; thus, we cannot completely exclude the possibility that we may have included cases of *R. felis* infection, whose clinical manifestations closely resemble those of MT. However, no *R. felis* case has been reported in Greece to date. Finally, given the observational nature of the study, we had no control over the different treatment options received by our study patients. Sample sizes were biased towards treatment with doxycycline and few patients were treated with ofloxacin or doxycycline plus ofloxacin, but our analysis did detect a statistically significant difference in times to defervesce. Although this difference is not likely to derive either from a varying age distribution or from differences in treatment initiation times, we cannot exclude the possibility that residual confounding by other factors could have affected the reported findings.

In conclusion, the early diagnosis of MT needs a high index of suspicion and depends on the ability of clinicians to identify specific clinical and laboratory features of the disease. The results of the present study provide enhanced knowledge of the clinico-epidemiological profile of MT, increasing the ability of clinicians to promptly respond to the disease. The study findings also emphasize that MT has the potential to cause significant morbidity. Awareness of the disease in endemic areas and the early administration of effective treatment are key factors to prevent potentially severe complications of MT.

Conflict of interest: The authors have no conflicts of interest to disclose.

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